REMARKS

Upon entry of the foregoing Amendment, Claims 1, 3-6, 8, 12, 13, 15 and 20 will remain pending in the application. Claims 7 and 21-22 have been canceled. Claims 1 and 15 have been amended. Support for the amendment of Claim 1 can be found at least in the original Claims 7, 21 and in the Specification on page 7, lines 2-9. Support for the amendment of Claim 15 can be found at least in the original Claims 18 and 22. These changes do not introduce new matter, and their entry is respectfully requested.

In the Office Action dated May 5, 2009, the Examiner sets forth a number of grounds for rejection. These grounds are addressed individually and in detail below.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 3-8, 12, 13, and 21 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner alleges the methotrexate:albumin molar ratio range recited at Claim 1, line 5, and particularly that portions of the range embracing methotrexate:albumin molar ratios of less than 1:1 and 1:1000, are unclear. Claim 1 has been amended to recite "... at a methotrexate:albumin molar ratio of 0.9 to 1.1:1. Applicant respectfully submits that molar ratios are conversion factors that can be used to relate the number of moles of a particular reactant needed to completely react with a certain number of moles of a second reactant. Therefore, the term "moles" cannot always be equated to the term, "molecule", wherein it is known in the art to have molar ratios ranging from less than 1:1.

Applicant respectfully submits that the grounds for the rejection have obviated, and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1, 3-8, 12 and 13 stand rejected under 35 U.S.C. § 103(a) over the Wolff et al. (hereinafter "Wolff") (Blood, Vol 102, No.11, page 404b) in view of Dave et al. (hereinafter "Dave") (U.S. Patent No. 6,491,923) and Stehle et al. (hereinafter "Stehle") (Anti-Cancer Drugs, Vol.8, pages 677-685) for the reasons set forth on pages 2-3 of the Office Action. Applicant respectfully traverses the rejection.

Amended independent Claim 1 is drawn to a method for preventing a transplantation-associated immune response in a subject, comprising: administering to said subject an effective amount of a conjugate comprising methotrexate and albumin at a methotrexate:albumin molar ratio of 0.9 to 1.1:1, wherein said transplantation is an organ transplantation selected from the group consisting of kidney, heart and liver transplantation.

As the Examiner indicated in the outstanding Office Action that the Wolff reference is limited to the allogeneic transplantation of bone marrow cells and spleen T-cells, and it does not anticipate or render obvious of Applicant's Claim 21 which was drawn to kidney, heart, or liver transplantation.

Applicant has amended Claim 1 to incorporate the limitations of the allowable Claim 21 and Claim 7. Therefore, Claim 1 is patentable over Wolff, Dave and Stehle. Claims 3-6, 8, 12 and 13 are also patentable since they depend directly or indirectly from Claim 1 and recite additional limitations.

Claims 15, 20, and 22 stand rejected under 35 U.S.C. § 103(a) over the Sutton et al. (hereinafter "Sutton") (US Patent No. 5,993,805) in view of the Sinkule et al. (hereinafter "Sinkule EP Application") (European Patent Application No. EP0282057) or Low et al.

(hereinafter "Low") (US Patent No. 5,688,488), for the reasons set forth on pages 3-6 of the Office Action.

To establish a *prima facie* case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka,* 490 F. 2d981, 180 USPQ 580 (CCPA, 1974).

The present independent Claim 15, as amended, is directed to a method for preparing a conjugate comprising methotrexate and albumin, said method comprising: activating a carboxyl group-containing methotrexate with 1-ethyl-3-(3-dimethylaminopropyl) carbonyldiimide in an organic solvent; and reacting the activated carboxyl group-containing methotrexate with albumin at a methotrxate:albumin molar ratio of **1.5:1 to 1:1.5**.

In contrast, Sutton generally describes the production of a methotrexate/albumin conjugate. However, Sutton does not teach or suggest reacting activated methotrexate with albumin at a methotrexate:albumin molar ratio of 1.5:1 to 1:1.5, as recited in Claim 15.

Sinkule and Low do not cure the deficiency of Sutton. Sinkule generally describes a method for coupling methotrexate to an antibody. Nonetheless, Sinkule neither mentions coupling methotrexate to albumin nor a methotrexate:albumin molar ratio of 1.5:1 to 1:1.5 as claimed.

Low generally describes a method for enhancing transmembrane transport of a diagnostic agent across a membrane of a living cell. Nevertheless, Low never mentions the production of a methotrexate albumin conjugate by using the molar ratio of 1.5:1 to 1:1.5 as recited in Claim 15.

For this reason alone, Claim 15 is patentable over Sutton, Sinkule EP Application and Low because these references, individually or in combination, fail to teach or suggest all of the claim limitations.

In addition, as discussed above, Sutton, Sinkule EP Application and Low fail to disclose the production of a methotrexate albumin conjugate by using the molar ratio of 1.5:1 to 1:1.5 as recited in Claim 15. Even if a skilled artisan had a desire to obtain methotrexate albumin conjugates with the molar ratio near 1:1, a skilled artisan would start from the highest possible loading of carrier albumin since one would have assumed that a considerable excess of the active agent would be required. Consequently, the present Claim 15 enables an almost complete conversion of the reactants, without a loss of one of the two reaction partners. One skilled in the art would would not be able to produce the Claim 15 based on Sutton, Sinkule EP Application and Low without undue experimentation. Thus, it is not obvious to one skilled in the art to derive the present invention from the prior art of record.

Accordingly, Claim 15 is patentable over Sutton, Sinkule and Low. Claim 20 is patentable over Sutton, Sinkule and Low because it depends from Claim 15 and recites additional patentable subject matter.

In view of the foregoing, Sutton, Sinkule and Low do not support a *prima facie* case of obviousness. Applicant respectfully submits that the grounds for the rejections have been obviated and withdrawal of the rejections under 35 U.S.C. § 103 (a), is respectfully requested.

Allowable Subject Matter

Applicant would like to thank the Examiner for the indication that Claim 21 would be allowable if rewritten to overcome the rejection under 35 U.S.C. § 112, 2nd paragraph, as set forth in the outstanding Office Action and to include all of the limitations of the base claim and any intervening claims.

Applicant has incorporated the limitations of the allowable Claim 21 and Claim 7 into Claim 1 and amended the methotrexate:albumin molar ratio range which obviates the grounds for the rejection under 35 U.S.C. § 112, second paragraph. Claims 3-6, 8, 12 and 13 are also patentable since they depend directly or indirectly from Claim 1 and recite additional limitations. Therefore, Claims 1 Claims 3-6, 8, 12 and 13 are in condition for allowance.

CONCLUSION

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to contact Applicant's counsel, Ping Wang, M.D. (Reg. No. 48,328), at 202.842.0217.

Respectfully submitted,

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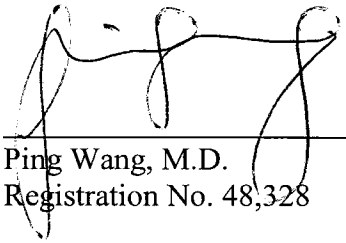

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